



Anesthesia for the Patient with Fibrodysplasia Ossificans Progressiva

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Learning Points

- FOP is a rare genetic disorder that leads to heterotopic ossification and progressive disability in the affected patient.
- Peri-operative care for the surgical patient with FOP requires a multidisciplinary approach to optimize patient safety and outcomes
- General anesthesia with awake nasotracheal intubation is considered to be standard of care for securing the airway of a patient with FOP
- Steroid administration is critical for the prevention of flare-ups precipitated by surgical stress
- Regional and neuraxial analgesia may be difficult or impossible in the surgical patient with FOP, requiring careful administration of multimodal analgesia to facilitate extubation and discharge

Introduction

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder causing progressive heterotopic ossification of connective tissue such as muscles, tendons, and ligaments, progressively

leading to the formation of a heterotopic skeleton [1]. Heterotopic bone formation causes ankylosis of joints throughout the body, progressively leading to loss of mobility and joint function, and severe disability. Any traumatic incident to connective tissue like a fall or invasive medical procedure, or a systemic medical illness such as influenza, has the potential to trigger an episode of muscle swelling and inflammation, known as a flare-up [2]. Rapid ossification with heterotopic bone formation may follow this period of inflammation, leading to progressively worsening disability. Throughout childhood and young adult life, bone formation is episodic, progressive, and extensive, progressively immobilizing all of the joints of the normotopic skeleton, rendering movement largely impossible. Flare-ups tend to be observed in a well-defined spatial pattern, causing extra-articular ankyloses of the joints of the axial and appendicular skeleton, immobilizing the patient in a 'new' skeleton of heterotopic bone [2]. Diagnosis of FOP is usually based on clinical examination and evaluation, which should lead to genetic confirmation. Unfortunately due to the rare nature of the disease, an affected patient may be initially misdiagnosed with a different disorder, leading to a delay in diagnosis. Common differential diagnoses include cancer and fibrosis, which may lead to the inappropriate performance of a biopsy of a lesion of ossification, which can cause detrimental flare-ups in the affected patient [3].

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Genetic Basis of Disease

FOP has a prevalence of approximately 1–2/1,000,000. A mutation mapped to the gene *ACVR1* on chromosome 2q23–24 has been identified as being responsible for causing FOP [4–6]. The gene encodes instructions for producing the protein activating receptor type-1. This protein is part of the family of bone morphogenetic protein type I receptors, found in many body tissues such as skeletal muscle and cartilage. Autosomal dominant inheritance is observed, but most cases are caused by spontaneous mutation. Approximately 97% of patients with FOP have this recurrent mutation, and 3% of affected individuals have a variant mutation in *ACVR1* [6]. The mutated gene causes abnormal activation of *ACVR1*, which leads to the production of heterotopic ossification of the affected individual's connective tissue. No ethnic, racial, gender, or geographic predilection to FOP has been identified [6]. Patients with classic clinical features of FOP demonstrate great toe malformations and progressive heterotopic ossification in a characteristic anatomic pattern [2]. These patients have been found to carry the same heterozygous mutation in the activation domain of *ACVR1*. Atypical FOP patients have also been described in the literature. Kaplan et al. formed two classes of these patients with clinical features unusual for FOP, classified as FOP-plus and FOP variants. FOP-plus patients are described as having classic defining features of FOP, plus one or more atypical features. These atypical features may include intraarticular synovial osteochondromatosis of hips, degenerative joint disease of hips, mild cognitive impairment, childhood glaucoma, cerebellar abnormalities, and diffuse cerebral dysfunction, among other features [6]. FOP variants have major variations in one or both of the two classic defining features of FOP. A study of 112 FOP patients demonstrated that 104 were sporadic cases, and 8 were familial cases [2]. Classic FOP was found in 82 sporadic cases and 7 familial cases, while 20 sporadic cases and 1 familial case had atypical disease. Some patients with atypical clinical presentation of FOP were found to have alternate mutations in the *ACVR1* gene. The classic missense or in-frame deletion occurs in most patients

with FOP-plus, however, some patients with FOP-plus may also have novel mutations explaining their additional features. FOP variant patients were also found to have a novel mutation.

Clinical Features and Management

FOP is an incurable progressive disease, with sporadic or triggered episodes and flare-ups of painful soft tissue swellings. Children born with FOP appear normal at birth, with the exception of a congenital malformation of the great toes [6]. If the diagnosis FOP is suspected, it is critical that all elective surgeries, biopsies, and intramuscular immunizations be delayed until a definitive diagnosis is made, to prevent the precipitation of flare-ups [7]. Progressive episodes of heterotopic ossification occur in specific patterns, usually first manifested as ossification of the dorsal, axial, cranial, and proximal regions of the body. Ventral appendicular, caudal, and distal regions tend to follow. The cervical spine often becomes ankylosed early in life, with fusion of the facet joints between C2 and C7. Misdiagnosis of ossification sites as tumor or fibrosis may lead to attempts at removal. This can result in rapid and progressive ossification and painful flare-ups. Any trauma can produce a flare up of ossification, such as minor soft tissue injury, muscle injury, intramuscular injection for immunization, and injections for dental work. As patients become progressively immobile, they tend to become wheelchair-bound by the end of the second decade of life [6]. It is important to note that the diaphragm, tongue, extra-ocular muscles, and cardiac muscle are all spared from the disease.

Progressive immobility and ankylosis can lead to additional life-threatening manifestations and complications of disease. Malnutrition, weight loss, and dehydration may result from ankyloses of the jaw and inability to open the mouth. Orthotopic ankyloses of the costovertebral joints, in addition to ossification of intercostal and paravertebral muscles is common. One study of 40 FOP patients demonstrated 65% of subjects having radiographic evidence of scoliosis [8]. Progressive heterotopic ossification in the paravertebral musculature, in combination with the

development of kyphoscoliosis, may lead to thoracic insufficiency syndrome (TIS) [6, 7]. Worsening TIS may progress to severe restrictive lung disease, hypoxia, pulmonary hypertension, and right-sided heart failure. Recurrent pneumonia and bronchiectasis is also seen in patients with TIS, due to difficulty with pulmonary toilet. Table 41.1 displays a full range of signs and symptoms which may be seen in the affected patient. Appropriate and timely immuni-

zation is critical for prevention of disease such as influenza and pneumonia, which themselves may cause flare-ups or progress to fatal illness. Intramuscular injection, though, must be avoided due to the risk of producing a flare-up. Instead, vaccinations should be administered by alternative routes [7].

At present, there is no definitive medical treatment for FOP. Flare-ups of painful inflammation and ossification have been demonstrated to have an inflammatory component, involving macrophages, lymphocytes, and mast cells in early FOP lesions [9]. Because of this inflammatory and immune component of flare-ups, corticosteroids are indicated as first-line treatment at the beginning of such episodes [7]. A 4-day course of high-dose corticosteroids, equivalent to 2 mg/kg/day of oral prednisone, should be started within the first 24 h of a flare up [7]. Experts recommend that use of corticosteroids be restricted only to extremely early symptomatic treatment of flare-ups affecting major joints, the jaw, and the submandibular area. Additionally, corticosteroids are recommended for prevention of flare-ups following major soft tissue injury, and for the prevention of flare-ups in elective or emergent surgery. Many flare-ups are extremely painful, and may require oral/topical NSAIDs and/or muscle relaxants. It is recommended to avoid narcotic analgesia whenever possible [7].

As there is no definitive treatment for FOP, affected individuals have a considerably shortened lifespan [10]. In a large review of mortality reports from two large registries of known FOP patients, 60 deaths were reported during a 33 year period. The median age at the time of death for these patients was 40 years. In this review, the two most common causes of death in patients with FOP were cardiorespiratory failure from TIS (54%) and pneumonia (15%).

Table 41.1 Signs and symptoms of FOP; adapted from Online Mendelian Inheritance in Man [18]

Head and neck	<ul style="list-style-type: none"> • Sensorineural and/or conductive hearing loss • Jaw fixation • Widely spaced teeth
Pulmonary	<ul style="list-style-type: none"> • Restrictive lung disease • Thoracic insufficiency syndrome • Respiratory failure
Skull	<ul style="list-style-type: none"> • Flat, broad mandibular condyles
Spine	<ul style="list-style-type: none"> • Progressive cervical vertebral spine fusion, with small cervical vertebral bodies • Scoliosis
Limbs	<ul style="list-style-type: none"> • Painful swellings in tendons, progressive ectopic ossification of tendons and ligaments • Broad femoral neck • Proximal medial tibial osteochondromas • Joint immobility
Hands	<ul style="list-style-type: none"> • Short thumb • Short first metacarpal • Fifth finger clinodactyly
Feet	<ul style="list-style-type: none"> • Short hallux, hallux valgus • Malformed first metatarsal^a • Monophalangism of first metatarsal
Skin, Nails, Hair	<ul style="list-style-type: none"> • Alopecia
Muscle, Soft Tissues	<ul style="list-style-type: none"> • Painful swelling in aponeuroses and fasciae • Progressive ectopic ossification of neck, dorsal trunk, proximal limbs, sternocleidomastoid, and masseters
Neurologic	<ul style="list-style-type: none"> • Asymptomatic hamartoma-like lesions in dorsal medulla and pons • Bulging of dorsal pons • Thickened pontomedullary junction and enlarged medulla • Enlargement of origin of vestibulocochlear nerves • Rarely mental retardation

^aThis classic sign is usually present at birth, and can help with making an early diagnosis of the disorder

Anesthetic Management

Pre-admission Evaluation

The patient with FOP may present to surgery for a variety of reasons. For example, affected indi-

viduals may present for a variety of periodontal procedures, including dental rehabilitation, extraction of teeth, and drainage of oral abscesses. As temporomandibular joint ankylosis results in very limited mouth opening, affected individuals often have difficulty with maintaining oral hygiene, necessitating periodontal surgery. Whenever possible, a multi-disciplinary team should be involved in the peri-operative care of the patient with FOP, including an appropriate surgical presence (such as a dentist or an oral and maxillofacial surgeon), an anesthesiologist, and an otolaryngologist [11, 12]. Additional consultation from a pulmonologist or cardiologist may be useful in the patient with significant cardiorespiratory dysfunction. A pre-admission anesthetic assessment prior to the date of surgery is critical in establishing disease course and severity. A thorough history and physical examination should be performed, with particular emphasis on examination of the airway and assessing cardiorespiratory function. Affected individuals may have limited or minimal mouth opening secondary to ankylosis of the temporomandibular joint. Cervical spine involvement, causing limited or absent neck flexion and extension, may further complicate airway management. Room air pulse oximetry can be a useful metric of baseline gas exchange in the patient, and should be performed prior to surgery. Additionally, auscultation of the chest wall and precordium can elicit signs of respiratory illness or cardiovascular decompensation. Useful laboratory workup may include a complete blood count and basic metabolic panel. Chronic hypoxemia may cause secondary erythrocytosis, with an increased hemoglobin and hematocrit, while an elevated bicarbonate level may indicate a chronic compensated acid-base disturbance. Additionally, longstanding malnutrition may result in a derangement of sodium, potassium, and chloride, further highlighting the potential relevance of pre-operative lab work.

Intravenous Access

Patients should be encouraged to drink clear liquids up to 2 hrs prior to surgery, to prevent further

dehydration from a traditional NPO from midnight approach. Difficulty with obtaining intravenous access should be expected, given that the affected patient may be dehydrated and may have musculoskeletal deformities further complicating anatomical assessment of peripheral veins. Extra care should be taken when securing intravenous access, and the use of ultrasound may be necessary. Although intramuscular injection is contraindicated in affected individuals, intravenous insertion can be well tolerated with the minimization of attempts and tourniquet time, and choosing a superficial vein if possible [7]. The smallest intravenous catheter appropriate for the procedure should be used [7]. Once intravenous access is obtained, administration of an antimuscarinic such as glycopyrrolate should be considered, to reduce airway secretions which may complicate later airway topicalization and intubation.

Airway Management

The patient with FOP presents many risk factors for difficulty with ventilation and intubation. Ankylosis of the temporomandibular joint may produce limited mouth opening and jaw prognathation, while involvement of the cervical spine may severely reduce the patient's ability to flex and extend their neck. Ossification of the strap muscles of the neck can also potentially complicate obtaining emergent front-of-neck access for a surgical airway if needed. Affected individuals may have respiratory compromise and little functional residual capacity, resulting in a shortened time period for desaturation following apnea. When considering the above risks, the recommended standard for airway management in the patient with FOP who requires general anesthesia is an awake nasotracheal intubation with fiberoptic bronchoscopy [7]. It is further recommended that a highly-skilled FOP-aware anesthesiologist be present for all elective intubations [7]. The use of local anesthetic for surgical anesthesia is often not an option for the surgical patient with FOP for a variety of reasons. For example, routine injections of local anesthetic for

dental procedures, specifically the use of mandibular blocks, should not be used due to the potential for rapid ossification of the pterygoid muscles, producing ankylosis of the temporomandibular joint [13]. Any injection of local anesthetic at any body site has the potential to precipitate a disease flare-up. Depending on the severity of disease, the presenting patient may or may not have limited mouth opening. Regardless of the ability to open the mouth, experts recommend that the nasal route for intubation is used, as opposed to orotracheal intubation [7]. Stretching of the pharyngeal and neck muscles, with potential trauma at the temporomandibular joint associated with direct or video laryngoscopy, may precipitate a future flare-up. A large case series describing the anesthetic records of 42 general anesthetics for 30 patients with FOP undergoing dental procedures highlights many of the significant considerations necessary when performing a general anesthetic for the patient with FOP, and recommendations made in this section are largely based on a review of this case series in conjunction with other available case reports in the literature [12]. General anesthesia was administered to all of the patients for their procedures, and in 34 of 42 cases, awake nasotracheal intubation was performed, with one intubation being orotracheal and another patient presenting to surgery with a pre-existing tracheostomy.

Care should be taken when achieving airway topicalization for an awake nasotracheal intubation. It may be difficult or impossible to perform targeted nerve blocks for the purposes of topicalization due to limited mouth opening. Additionally, there is a potential risk of precipitating a disease flare up with the targeted injection of local anesthetic, such as in a transtracheal block. Given these important considerations, utilizing alternative methods for airway topicalization may be preferred. These methods may include 4% lidocaine nebulization in the pre-operative holding area, nasopharyngeal airways lubricated with viscous lidocaine, and instillations of 4% lidocaine onto relevant airway structures via bronchoscopic visualization. Special attention should also be paid towards calculating

the safe dose of local anesthetic prior to airway topicalization, as the patient with FOP may be severely underweight, resulting in a much lower safe dose of local anesthetic. Prior to insertion of a nasopharyngeal airway, the use of a nasal decongestant agent, such as oxymetazoline or phenylephrine, to dilate the breadth of the nasal passage may be useful to prevent epistaxis and allow for easier passage of a fiberoptic bronchoscope. Epistaxis and subsequent laryngospasm during attempted nasotracheal intubation in the patient with FOP could prove catastrophic, due to potentially difficult or impossible front-of-neck access as a result of ossification in the neck, so every possible effort should be made to prevent this from occurring. Sedative medication may be used cautiously to help facilitate awake nasotracheal intubation, with consideration that the patient with FOP may be very sensitive to small doses of sedative medications. Maintenance of spontaneous respiration is paramount during the procedure, as mask ventilation may prove to be difficult if not impossible, and emergent front-of-neck access may be challenging. In this author's experience, a short-acting benzodiazepine is generally administered (midazolam 1–2 mg) in the pre-operative area. Once in the operating room, ASA standard monitors should be applied, including end-tidal sampling nasal cannula with supplemental oxygen. A low-dose infusion of remifentanyl or dexmedetomidine may then be started. If additional sedation is required, careful administration of ketamine may also be considered [7]. An experienced otolaryngologist should be available during airway management, and surgical airway equipment should be immediately available in the operating room [11].

Intraoperative Management

Monitoring

As for any surgical patient, ASA Standard monitors should be applied on presentation to the operating room, with consideration for additional invasive monitoring if the surgical procedure or patient's comorbidities necessitates. Application

of an oscillometric blood pressure cuff is safe in the patient with FOP, but may prove to be difficult due to ankylosis of the upper limbs, so consideration for alternative sites, such as the lower extremities, may be appropriate. Additionally, extra padding should be considered under the cuff to reduce the impact of frequent inflation of the cuff [7].

Positioning

Following successful nasotracheal intubation and administration of general anesthesia, special attention should be focused on ensuring safe patient positioning. Affected patient's joints may be fused in different rigid positions as a product of their disease state and ankylosis, so all pressure points must be padded appropriately, and the neck must be supported [12]. Steep trendelenburg positioning may be needed by the dentist or surgeon in the case of the patient who has a fused cervical spine, so ensuring safe positioning with appropriate padding is critical to ensuring a safe position for the patient while under a general anesthetic [11].

Steroid Administration

The International Clinical Council on FOP & Consultants recommends that steroid prophylaxis be used for dental and surgical procedures, due to the potent anti-inflammatory effects in conjunction with the inflammatory basis triggering FOP flare-ups [7]. Based on this recommendation, the surgical patient should receive methylprednisolone 50 mg IV q6hrs following induction of general anesthesia. Patients should then be continued on a 4 day regimen of oral prednisone per current guidelines once tolerating oral intake [7].

Maintenance Agents

Maintenance of general anesthesia with a volatile or intravenous anesthetic can safely be per-

formed, with particular emphasis on avoiding the administration of muscle relaxation if possible, to prevent the risk of residual neuromuscular block on emergence and extubation. If muscle relaxation is required, use of quantitative neuromuscular monitoring in combination with a novel reversal agent such as sugammadex should be considered, ensuring that appropriate reversal of neuromuscular blockade has been achieved. Administration of succinylcholine should be avoided, as affected patients may be largely immobile, and therefore the risk exists for catastrophic hyperkalemia following administration. The large case series by Kilmartin et al. reports the use of a maintenance anesthetic of sevoflurane in oxygen/air [11]. A review of nine case reports of patients with FOP undergoing general anesthesia report the safe use of several different volatile agents, including sevoflurane, isoflurane, desflurane, and enflurane [14].

Emergence and Extubation

The same precautions which were in place during intubation should be made available during extubation, including the immediate availability of fibre-optic bronchoscopy and surgical airway access. Planning for airway emergencies on tracheal extubation is highlighted by one case report of a patient who required emergent tracheostomy after failed attempts at re-intubation following extubation. (k) Extubation of the trachea should only be attempted once the patient is fully awake and following commands, with objective return of neuromuscular strength documented if a muscle relaxant was administered during the anesthetic.

Patient Disposition

The multidisciplinary team caring for the surgical patient with FOP should have a low threshold to consider post-operative inpatient admission for continued respiratory monitoring and pain management, although this may vary widely depending on the surgical procedure performed.

It is certainly possible, though, to achieve same-day discharge in patients presenting for uncomplicated dental procedures. In the case series by Kilmartin et al. 36 of 42 case were discharged home on the same day as their dental procedure, with no significant postoperative complications encountered [11]. In this case series, reasons for admission were brittle diabetes, a history of malignant hyperthermia, worsening hypoxia post-extubation, concern for development of airway edema. One patient was also admitted due to the presence of multiple medical comorbidities with a history of a difficult airway and tracheostomy [11].

Perioperative Pain Management

Pain management can be challenging in the patient with FOP, especially for those patients who are maintained on outpatient opioid medications. Acetaminophen and nonsteroidal anti-inflammatories should be utilized in all appropriate patients following discussion with the surgical team. Opioid medications should be minimized to avoid post-operative respiratory depression potentially leading to catastrophic respiratory arrest. The use of intravenous ketamine, in an effort to spare opioids, may be considered in appropriate patients [7]. Epidural analgesia for peri-operative analgesia can prove to be difficult if not impossible, due to advanced ossifications at the thoraco-lumbar area. Attempting epidural or spinal analgesia is also relatively contra-indicated in affected patients, due to the risk of precipitating a flare-up [7]. The performance of superficial nerve blockades with local anesthetic has been described in the literature, and this technique may be utilized in appropriate patients for specific surgical procedures, as strict subcutaneous injections have a low potential for the development of heterotopic ossification [15]. Schober et al. reported the successful use of ultrasound-guided ankle block in a 33 year-old woman with advanced FOP presenting with progressive osteomyelitis originating from the fifth digit of her foot [16]. In their report, continuous ultrasound guidance was used to avoid nee-

dle contact to muscles, tendons, and bones. Plain bupivacaine 0.5% was injected into the sites of the tibial and deep peroneal nerve sites. This was followed by a strict subcutaneous field block used to anesthetize the remaining three nerves. If additional analgesia is required, the use of patient-controlled analgesia (PCA) may be considered, with the use of supplemental oxygen and careful monitoring of oxygenation and ventilation [7].

Pregnancy and FOP

Report of pregnancy in FOP has occurred infrequently. Muglu et al. published a series of four cases of pregnancy in FOP [17]. Two patients successfully delivered an infant. One patient was a 27-year old woman with classic FOP and complete fusion of the neck, shoulders, elbows, hips, knees, and jaw. She had an emergency caesarean section at 30 weeks gestation under general anesthesia. A second patient was also a 27-year old woman with classic FOP, who as admitted in pre-term labor and had an emergency caesarean section. Given the difficulties associated with performing regional anesthesia, as well as potential for ossification in tracheal rings, the use of awake fiberoptic nasotracheal intubation remains the safest option for anesthetic management of the parturient, with a low threshold to keep the patient intubated post-operatively given the risk for post-operative airway edema and difficulty with reintubation [7].

Conclusions

FOP is a rare genetic disease causing progressive heterotopic ossification and disability in the affected patient, ultimately leading to early mortality. The patient with FOP who presents for elective surgery should be seen in advance by a multidisciplinary team, involving the surgical team, anesthesiology, and relevant medical subspecialties. Caution with airway management, and securing the airway via awake nasotracheal intubation is critical. With appropriate precau-

tion and care, it is possible to achieve successful peri-operative outcomes in the surgical patient with FOP.

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